ATTACHMENT C

REMARKS

By the present amendment, the claims have been amended in such a manner so as to overcome all outstanding rejections and to place the present application in condition for allowance. In particular, Claims 9, 15, 20, 22, 30 and 33 have been amended in such a manner as to overcome any objections to these claims, and new Claim 36 is also added which relates to subject matter disclosed and claimed in the application so that no new issues are raised. Claims 1, 3, 4, 6-7 and 34-35 remain in their previously presented form. All other claims have been canceled without prejudice. Accordingly, for reasons as stated below, the present amendments should be entered and this case should be allowed.

As an initial matter, the objection relating to the trademark designation for "Superose" has been overcome by the amendment to the specification provided herewith.

In the Official Action, the Examiner rejected Claims rejected Claims 9, 14, 15, 20-22, 24, 25, 29 and 33-35 under 35 U.S.C. § 112, first paragraph. This rejection is respectfully traversed. Claims 9, 14, 15, 20-22, 24, 25, 29 and 33-35 have been rejected under 35 U.S.C. § 112, first paragraph, as the specification is said to not enable any person skilled in the art to use the invention commensurate with the claims. Claims 14, 24, 25 and 29 have been canceled. Claims 9, 15, 20, 22 and 33 have been amended so as to overcome this rejection. As amended, the claims at issue refer to detection of anti-CV2 antibodies and not to diagnosis of a neurological syndrome or diagnosis of a tumor. The Examiner has stated that claims 33-35 are drawn to a kit that

cannot be used to diagnose a disease or disorder other than neuropathic paraneoplastic syndromes, and this objection is overcome by the amendments to claim 33.

The Examiner has stated that claims 24 and 29 are directed to a genus of peptides that includes members that, although capable of binding anti-CV2 antibodies, differ structurally from the polypeptide of SEQ ID NO:8, and are not necessarily fragments of the polypeptide of SEQ ID NO:8. Without addressing the Examiner's arguments in this regard, Claims 24 and 29 have been canceled without prejudice.

In the Official Action, the Examiner rejected Claims rejected Claim 14 under 35 U.S.C. § 112, second paragraph, as it is said to be indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In addition, the Examiner states that "the blood sample" lacks antecedent basis. Without addressing this argument, the rejection has become moot because Claim 14 has been canceled.

In the Official Action, the Examiner rejected Claims 1, 9, 10, 14, 20, 21, 24, 25, 29 and 30 under 35 U.S.C. § 102(b), as it is said they are anticipated by Honnorat *et al.* (*J. Neurol. Neurosurg. Psych.* 1996; 61:270-278) as evidenced by Honnorat *et al.* (*Eur. J. Neurosci.* 1999 Dec; 11(12):4226-4232). Claims 14, 24, 25 and 29 have been canceled. Claims 9, 20 and 30 have been amended. These rejections are traversed for the reasons that follow.

Honnorat *et al.* (1996) teaches that 9 of 11 serum samples from patients with paraneoplastic neurological syndromes (PNS) contained antibodies that bound to a 66 kD protein found in human embryo brain, and 6 of the 11 serum samples contained antibodies that bound to a 66 kD protein found in adult human brain. Honorat *et al.*

(1996) did not characterize these proteins beyond estimating an apparent molecular weight from their migration by polyacrylamide gel electrophoresis.

The Examiner states, "Honnorat *et al.* (1996) teaches a composition comprising a purified polypeptide that is 66 kDa, which is produced by human brain cells and binds anti-CV2 antibodies." (See Office Action of 22 November 2004.) The Examiner further states (Office Action of 6 April 2005), "Honnorat *et al.* (1999) provides factual evidence that the protein isolated by Honnorat *et al.* (1996) is the same as the protein that is described by Honnorat *et al.* (1999)." The Examiner does not explain what the factual evidence is. How do we know that the 66 kD human protein seen in Honnorat *et al.* (1996) is the same human protein that was encoded in ATCC clone number 469253 as reported in Honnorat *et al.* (1999)? Honnorat *et al.* (1999) do not produce the human Ulip4/CRMP3 protein for which they show an amino acid sequence, and test its physical properties or binding characteristics to antibodies.

The Ulip4 protein has been called CRMP3 by other researchers. See, for example, Figure 5 on page 4230 of Honnorat *et al.* (1999). It has become clear in the years following the invention that Ulip4/CRMP3 is one of a family of homologous proteins of similar molecular weights. See Table 1, page 5 in WO 02/02620 (copy enclosed). Due to the extensive homology among the proteins, antibodies to one of the proteins could be expected to cross-react with other proteins in the family. Therefore, it is not scientifically justified to conclude that the proteins described in Honnorat *et al.* (1996) and in Honnorat *et al.* (1999) are the same proteins.

The Examiner quotes *The Manual of Patent Examining Procedure* to point out the exception to the rule that the critical reference date must precede the filing date of the application:

> In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include characteristics and properties of a material or a scientific truism. MPEP § 2124.

The Examiner is using Honnorat *et al.* (1999) not for the fact that all proteins have an amino acid sequence. Rather, the Examiner has taken from Honnorat *et al.* (1999) the conclusion that the 66 kD human brain protein which bound antibody from some patients with anti-CV2 antibodies in Honnorat *et al.* (1996) is a protein with amino acid sequence SEQ ID NO:8. This is not a universal fact or a scientific truism. It is improper to use Honnorat *et al.* (1999) in this way for this conclusion.

Further, the citing of Honnorat *et al.* (*Eur. J. Neurosci. 11(12)*: 4226-4232 (1999)) is not permissible for a second reason. Honnorat *et al.* 1999, published after the filing date of the application, describes the work of the inventors, and to a large extent shares the content of the application. Thus, the Examiner is, in effect, using the teaching of the application itself to support an allegation that a teaching in Honnorat *et al.* 1996 shows an inherent characteristic.

To the contrary, the 66 kD protein seen by Honnorat *et al.* (1996) cannot be characterized as a purified ULIP polypeptide comprising the amino acid sequence SEQ ID NO:8. Therefore, claims 1, 9, 10, 20, 21, and 30 are not anticipated. Regarding

claim 30, Honnorat *et al.* (1996) does not disclose a fragment of a purified ULIP polypeptide comprising amino acid sequence SEQ ID NO:8.

In the Official Action, Claims 30-32 were rejected under 35 U.S.C. § 102(b) as being anticipated by Antoine *et al.* (*J. Neurol. Sci.* 1993; 117(1-2):215-223) as evidenced by Honnorat *et al.* (*Eur. J. Neurosci. 11(12)*: 4226-4232 (1999). Claims 31 and 32 were canceled previously. Claims 30 and 33 have been amended. This rejection is respectfully traversed for the reasons that follow.

Antoine *et al.* describe tests of serum from a woman with paraneoplastic encephalomyelitis and undifferentiated carcinoma. The serum contained antibodies to proteins of 44, 59 and 135 kDa in extracts of human cerebellum, according to the results of western blot experiments. See page 220, section subtitled "Western blot." There is no indication in Antoine *et al.* that the serum from a patient with paraneoplastic neurological syndrome (PNS) contains antibodies that bind to a 66 kDa human protein, a protein with amino acid sequence SEQ ID NO:8 or a peptide comprising a fragment of a purified polypeptide with SEQ ID NO:8.

Figure 2G of Antoine *et al.* shows indirect immunofluorescence testing of the woman's serum on fixed human brainstem and cerebellum. The result was staining of "rare immuno-positive cells with small cytoplasm and short processes." See page 219, section subtitled "Human brain." There is no evidence at all that a peptide comprising a fragment of a polypeptide comprising SEQ ID NO:8 was attached to a solid support in the process of fixing human brain slices. There is no evidence in Antoine *et al.* that a fragment of a polypeptide comprising SEQ ID NO:8 can bind to anti-CV2 antibodies.

There is nothing to indicate that a peptide comprising a fragment of a polypeptide comprising SEQ ID NO:8 was present in any way.

The experiments of Antoine *et al.* do not show any human protein of 66 kDa or of amino acid sequence SEQ ID NO:8. Honnorat *et al.* (1999) cannot identify the proteins of Antoine *et al.* of 44, 59 and 135 kDa. Honnorat *et al.* (1999) does not demonstrate that a protein of SEQ ID NO:8 is produced in human brain or binds anti-CV2 antibodies. Honnorat *et al.* (1999) cannot demonstrate that a protein of SEQ ID NO:8 is inherently present in the fixed tissue samples in Antoine *et al.* There is nothing to connect the teachings of the two references.

Honnorat *et al.* (1999) showed that sera from patients with paraneoplastic neurological diseases (PND) contained antibodies that bound to HeLa cells transfected with Ulip4/CRMP3 cDNA encoding a fragment of mouse Ulip4. A human EST homologous to the mouse Ulip4/CRMP3 cDNA was found in a database search. Honnorat *et al.* (1999) did not disclose a peptide comprising a fragment of a polypeptide comprising SEQ ID NO:8 and cannot support any conclusions about such a peptide.

To explain the use of Honnorat *et al.* (1999) in the rejection, the Examiner has quoted *The Manual of Patent Examining Procedure*, pointing out the exception to the rule that the critical reference date must precede the filing date of the application:

> In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include characteristics and properties of a material or a scientific truism. MPEP § 2124.

The Examiner is using Honnorat *et al.* (1999) for concluding that "fixed sections of human brain comprise an endogenous 66 kDa polypeptide, which comprises the amino acid sequences set forth as SEQ ID NO:8, to which anti-CV2 antibodies bind." This is a conclusion that could not have been made before Honnorat *et al.* (1999) and the subject application. This is not a universal fact or a scientific truism.

Further, the citing of Honnorat *et al.* (*Eur. J. Neurosci. 11(12)*: 4226-4232 (1999)) is not permissible for a second reason. Honnorat *et al.* 1999, published after the filing date of the application, describes the work of the inventors, and to a large extent shares the content of the application. Thus, the Examiner is, in effect, using the teaching of the application itself to support an allegation that a teaching in Honnorat *et al.* 1996 shows an inherent characteristic.

In the Official Action, the Examiner rejected Claims 3, 6, 7, 15, 22 and 33-35 under 35 U.S.C. § 103(a), as it is said they are obvious over Honnorat *et al.* (*J. Neurol. Neurosurg. Psych.* 1996; 61:270-278) as evidenced by Honnorat *et al.* (*Eur. J. Neurosci.* 1999 Dec; 11(12):4226-4232), in view of US Patent No. 6,455,267. Claims 15, 22 and 33 have been amended. This rejection is respectfully traversed for the reasons that follow.

Honnorat *et al.* (1996) teaches that 9 of 11 serum samples from patients with PNS contained antibodies that bound to a protein found in human embryo brain. Six of the 11 serum samples contained antibodies that bound to a 66 kD protein found in adult human brain. Both the embryo brain protein and the adult human brain protein were seen to migrate as a protein of 66 kDa by polyacrylamide gel electrophoresis.

Honnorat *et al.* (1999) shows that sera from patients with paraneoplastic neurological diseases (PND) contained antibodies that bound to HeLa cells transfected with Ulip4/CRMP3 cDNA encoding a fragment of mouse Ulip4. A human EST homologous to the mouse Ulip4/CRMP3 cDNA was found in a database search.

US Patent No. 6,455,267 describes the cloning of cDNA encoding glutamic acid decarboxylase (GAD) and the use of GAD protein in the identification of autoantibodies to GAD present in the sera of diabetic patients.

Claims 3, 6 and 7

The Examiner states (Office Action of 22 November 2004, page 30, lines 16-20):

> However, Honnorat *et al.* (1996) does not expressly teach an isolated nucleic acid molecule comprising a polynucleotide sequence encoding the disclosed polypeptide (claim 3); nor does Honnorat *et al.* expressly teach a cloning and/or expression vector comprising a polynucleotide sequence encoding the polypeptide (claim 6) or a host cell transfected with such a cloning or expression vector (claim 7).

While the Examiner is correct in these statements, the Examiner has concluded that the human protein that appeared as a band at the position of a protein with molecular weight 66 kDa, and bound to antibodies found in serum from patients with PND is necessarily the same protein discussed in Honnorat *et al.* (1999). This conclusion is based on the assumption that there is one and only one human brain protein of apparent molecular weight 66 kDa that binds to antibodies found in serum from patients with paraneoplastic neurological diseases, or that only one type of antibody, which binds to one protein of apparent molecular weight 66 kDa, is present in the serum of all patients with paraneoplastic neurological diseases. Both assumptions

have no support in the prior art or in knowledge that could be attributed to one of ordinary skill in the art.

Moreover, Honnorat *et al.* 1999, is not available as a reference to cite for a specific teaching regarding the invention which also appears in the specification. Honnorat *et al.* 1999, published after the filing date of the application, describes the work of the inventors, and to a large extent shares the content of the application. Thus, the Examiner is, in effect, using the teaching of the application itself to support an allegation that a teaching in Honnorat *et al.* 1996 shows an inherent characteristic.

The Examiner has concluded that the human protein that appeared as a band at the position of a protein with molecular weight 66 kDa, and bound to antibodies found in serum from patients with PND is necessarily the same protein discussed in Honnorat *et al.* (1999) and has amino acid sequence SEQ ID NO:8.

The Federal Circuit set forth the standards for anticipation by inherency:
A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. *Lewmar Marine, Inc. v. Barient Inc.*, 827 F.2d 744, 747 [3 USPQ2d 1766] (Fed. Cir. 1987). Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 [20 USPQ2d 1746] (Fed. Cir. 1991).

It is an inherent feature of proteins that they have an amino acid sequence. It is not an inherent feature (that is, it is not *necessarily* a feature) of every brain protein that migrates as a 66 kDa protein by polyacrylamide gel electrophoresis that it must have SEQ ID NO:8 as its amino acid sequence. Honnorat *et al.* (1996) discloses a band on a

gel migrating at an apparent molecular weight of 66 kDa. Without specific amino acid sequence information obtained from this very protein, it cannot be deduced that this protein has amino acid sequence SEQ ID NO:8.

The teachings of US 6,455,267 do not help to identify the protein of Honnorat *et al.* (1996) as having amino acid sequence SEQ ID NO:8 or in identifying any nucleic acid that could encode a polypeptide with SEQ ID NO:8. Therefore, the combined teachings of Honnorat *et al.* (*J. Neurol. Neurosurg. Psych.* 1996; 61:270-278) as evidenced by Honnorat *et al.* (*Eur. J. Neurosci.* 1999 Dec; 11(12):4226-4232), in view of US Patent No. 6,455,267 cannot make obvious the invention of claims 3, 6 and 7.

The Examiner states further (Office Action of 22 November 2004, page 31, lines 24-30):

> Furthermore, it would have been prima facie obvious to one ordinarily skilled in the art at the time of the invention to produce a host cell transfected with a vector comprising a polynucleotide sequence encoding the polypeptide disclosed by Honnorat *et al.*, because '267 teaches such host cells can be used to produce the polypeptide. One ordinarily skilled in the art at the time the invention was made would have been motivated to make and use such kits to facilitate the production of the polypeptide for use in making the diagnostic kits.

The Examiner again relies on Honnorat *et al.* (1999) for the conclusion that the 66 kD human brain protein which bound antibody from some patients with anti-CV2 antibodies in Honnorat *et al.* (1996) is a protein with amino acid sequence SEQ ID NO:8. Honnorat *et al.* (1999) does not make possible the unambiguous identification of the 66 kDa human brain protein of Honnorat *et al.* (1996) as a protein with amino acid sequence SEQ ID NO:8. Furthermore, the use of Honnorat *et al.* (1999) is not permissible, as has been presented above. Without knowledge of the amino acid

sequence SEQ ID NO:8, it would not have been possible to describe the inventions of claims 3, 6 and 7, no matter which other references Honnorat *et al.* (1996) is combined with.

Claim 22

The Examiner states in the Office Action of 22 November 2004, page 31, lines 2-4):

> '267 teaches that either the intact protein to which the autoantibodies bind or an antigenic fragment thereof to which the antibodies bind can be used in the methods; see, e.g., column 3, lines 12-27.

The Examiner is again relying on the teachings of Honnorat *et al.* (1999). Without relying on Honnorat *et al.* (1999), one of ordinary skill in the art would not know the association of human ULIP4 with paraneoplastic neurological diseases, and would not have the necessary knowledge to provide a polypeptide comprising SEQ ID NO:8 or a fragment thereof as a component of a kit to test for binding of anti-CV2 antibodies. Reliance on the teachings of Honnorat *et al.* (1999) is not permissible, for reasons explained above. Honnorat *et al.* (1996) cannot unambiguously identify the band of protein seen migrating as a 66 kDa protein as having SEQ ID NO:8. The teachings of US Patent No. 6,455,267 cannot provide the specific information to conceive of a kit for the diagnosis of paraneoplastic neurological syndromes, as it teaches nothing about PNS or any molecules associated with the pathology of PNS.

The Examiner cannot conclude as fact that the band seen by Honnorat *et al.* (1996) on a polyacrylamide gel migrating at an apparent molecular weight of 66 kDa consisted of one and only one protein that must have had amino acid SEQ ID NO:8. As reported in Honnorat *et al.* (1999) (see first paragraph of Discussion, page 4230) and in WO 02/02620 (see especially Table 1, page 5), the situation is far more complex. Anti-CV2 antibodies bind to more than one protein and a whole family of homologous proteins have a molecular weight that could cause them to migrate on a polyacrylamide gel at an apparent molecular weight of 66 kDa. One of ordinary skill in the art would be aware of the possibility of related proteins and cross-reactivity of antibodies.

Honnorat *et al.* (1999) did not extract the 66 kDa band from the gel of 1996, obtain the amino acid sequence of the protein, synthesize oligonucleotide primers based on the amino acid sequence and attempt to isolate a gene encoding that protein in the gel. The Examiner is only speculating to identify the 66 kDa band of Honnorat (1996) as having SEQ ID NO:8.

Claims 15 and 33-35

The Examiner states (Office Action of 22 November 2004, page 31, lines 13-23):

> It would have been prima facie obvious to one ordinarily skilled in the art at the time of the invention to produce and use a kit comprising either the intact polypeptide disclosed by Honnorat *et al.* or an antigenic fragment thereof that binds anti-CV2 antibodies for use in detecting anti-CV2 antibodies and diagnosing a paraneoplastic neurological syndrome and tumor associated therewith in patients, because Honnorat *et al.* teaches detecting anti-CV2 antibodies is diagnostic of such disease and '267 teaches such diagnostic kits for use in detecting such autoantibodies. One ordinarily skilled in the art at the time the invention was made would have been motivated to make and use such kits to facilitate the

diagnosis of a paraneoplastic neurological syndrome in which anti-CV2 antibodies are produced in patients and the tumor associated therewith.

Honnorat *et al.* (1996) defines anti-CV2 antibodies as those binding to a cytoplasmic antigen in a subpopulation of glial cells in the white matter (page 273, first paragraph of Results section). Honnorat *et al.* (1996) presents one experiment to test binding of antibodies in a human serum sample to human proteins in human brain extracts. Serum from one patient contained antibodies that bound to a 66 kDa band in both human and rat brain extracts. See legend to Figure 7(B).

US Patent No. 6,455,267 describes the cloning of cDNA encoding glutamic acid decarboxylase (GAD) and the use of GAD protein in the identification of autoantibodies to GAD present in the sera of diabetic patients.

Combining the references, Honnorat *et al.* (1996) and US 6,455,267, one of ordinary skill in the art might wish to develop an assay or assay kit to detect the antigen to which anti-CV2 antibodies bind. However, Honnorat *et al.* had not identified the brain protein to which anti-CV2 antibodies bind. Showing that there is a protein migrating at 66 kDa in brain extracts does not provide one of skill in the art with sufficient information to develop an assay or a kit to perform the assay.

The Examiner has used Honnorat *et al.* (1999) for concluding that "fixed sections of human brain comprise an endogenous 66 kDa polypeptide, which comprises the amino acid sequences set forth as SEQ ID NO:8, to which anti-CV2 antibodies bind." The conclusion that the 66 kDa polypeptide has SEQ ID NO:8 could not have been made before Honnorat *et al.* (1999). This is not a universal fact or a scientific truism, which in some circumstances, may be cited from a reference available as prior art

before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). See also MPEP § 2124.

Further, the citing of Honnorat *et al.* (*Eur. J. Neurosci. 11(12)*: 4226-4232 (1999)) is not permissible for a second reason. Honnorat *et al.* 1999, published after the filing date of the application, describes the work of the inventors, and to a large extent shares the content of the application. Thus, the Examiner is, in effect, using the teaching of the application itself to support an allegation that a teaching in Honnorat *et al.* 1996 shows an inherent characteristic.

In all cases, Applicants' amendments overcome the Examiner's prior rejections which should now be withdrawn.

One final objection, to Applicants' claim 20, has been overcome by the amendments to that claim.

In light of the amendments and arguments as set forth above, Applicants submit that upon entrance of the present amendment, the present application will be placed in condition for immediate allowance. Entrance of the amendment and allowance of this application is thus earnestly solicited.

END OF REMARKS